1,006,156

PATENT SPECIFICATION

NO DRAWINGS

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Int Cl.:—C 07 c, d

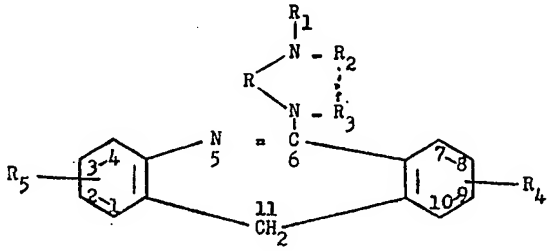
COMPLETE SPECIFICATION

6-Basic Substituted Morphanthridines

We, DR. A. WANDER S.A., a body corporate, organised under the laws of Switzerland, of 1'15 Monbijoustrasse Berne, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to with heterocyclic compounds showing an amidine structure.

According to the invention there are provided 6-basic substituted morphanthridines of the general formula:

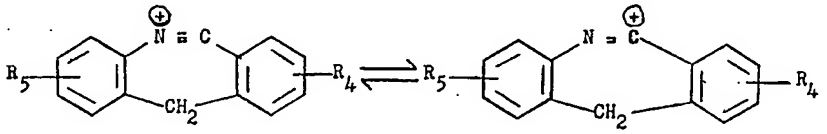


(I)

and physiologically acceptable acid addition salts thereof. In the formula I, R denotes a straight or branched chain alkylene group having not more than 5 carbon atoms; R_1 denotes a hydrogen atom or a lower alkyl, lower hydroxyalkyl, acylated lower hydroxyalkyl or alkoxyalkyl group having not more than 5 carbon atoms; R_2 and R_3, which may be the same or different denote hydrogen or lower alkyl, or, when taken together an ethylene group; and R_4 and R_5 which may be the same or different denote hydrogen or halogen. The term "lower" alkyl etc., is intended to mean alkyl etc. having from 1 to 3 carbon atoms.

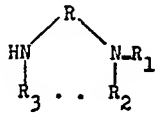
Preferred compounds according to the invention are those wherein the basic substituent in the 6-position is the 4-methyl-1-piperazinyl residue. Halogen substituents in the benzene nuclei are preferably in the 3- or 8-positions. Specific preferred compounds according to the invention are 6-(4-methyl-1-piperazinyl)-morphanthridine, 3-chloro-6-(4-methyl-1-piperazinyl)-morphanthridine and 6-(4-methyl-1-piperazinyl)-8-chloro-morphanthridine, and the physiologically acceptable acid addition salts thereof.

The compounds of this invention are obtained by reacting a reaction mixture containing nitrilium or imonium cations of the formulae:



(II),

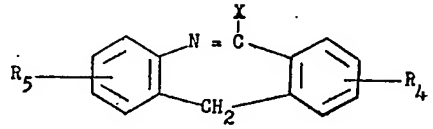
wherein R_4 and R_5 have the above-mentioned meaning, with an amine of the formula:



(III),

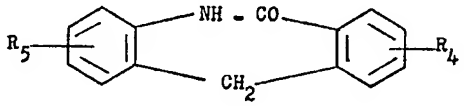
wherein R, R_1, R_2, and R_3 have the indicated meaning.

Nitrilium or imonium cations of formulae II can be regarded as dissociation products of compounds of the formula:



(IV),

wherein R_4 and R_5 have the above-mentioned meaning, and X represents a halogen atom, the sulfhydryl group, or an alkoxy or alkylthio group which is activated if required, e.g. the *p*-nitrobenzylthio group. Such compounds (IV) are obtained, for instance, by conversion of lactams of the formula:

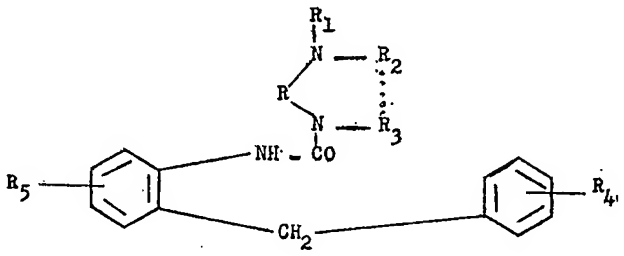


(V),

wherein R_4 and R_5 have the above-mentioned meaning, into the thiolactams, if required with subsequent alkylation of the latter, or by reacting the lactams (V) with a halogenating agent like phosphoroxychloride or phosphorus pentachloride, preferably in the presence of catalytic amounts of dimethylaniline or dimethylformamide. The lactams (V) can be obtained, for example, by ring closure of suitable *o*-isocyanato-diphenylmethanes with aluminium chloride. Depending upon the chemical nature of the residue X and also of eventual nuclear substituents, the IV compounds in the reaction mixture obtained are dissociated to a higher or lower degree into the nitrilium or imonium cations, so that the reaction mixtures can be used directly for reacting with the amine of formula III. In part the compounds of formula IV produced in this or in another manner can be isolated in undissociated form and then yield the desired nitrilium or imonium cations (II) upon dissolution in a suitable, preferably polar solvent, if required by heating and in the presence of the amine of formula III, which can also serve as a solvent. Reaction mixtures containing cations of formula II can also be produced, for example, by intramolecular Ritter's reaction (action of a nitrile group on a phenyl cation) in *o*-cyanodiphenylmethanes, by Beckmann's transformation of (if desired halogenated) anthronoximes, or by Schmidt's reaction of (if desired halogenated) anthrones with hydrazoic acid. Both the last-named reactions may lead, if the starting material consists of unsymmetrically halogenated anthronoximes or anthrones, to isomeric products which, if necessary, must be subsequently separated. In the said reaction mixtures the anionoid components

which may appear are—besides those derived from the substituent X of formula IV —, depending upon the mode of preparation of the cations (II), for example also anions of sulphuric, toluene-sulphonic, phosphoric, hydrofluoric, of hydrofluoboric acids, etc.

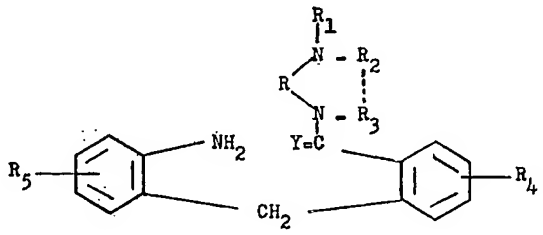
Compounds in accordance with this invention are also obtained by dehydration of urea derivatives of the formula:



(VI),

wherein R, R_1, R_2, R_3, R_4 and R_5 have the meaning indicated above, for instance through several hours' action by dehydrating agents, for example zinc dichloride, aluminium chloride, tin tetrachloride and phosphoric acid, but preferably phosphoroxychloride, if required in the presence of an inert solvent with a suitable boiling point, such as benzene or toluene.

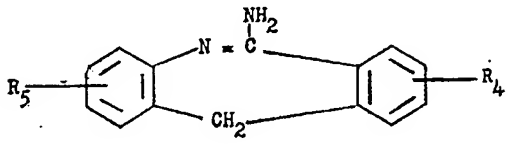
Compounds according to this invention are also obtained by ring closure, through intramolecular condensation, of acid amides or thioamides of the formula:



(VII),

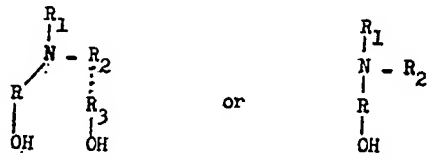
wherein R, R_1, R_2, R_3, R_4, and R_5 have the above-mentioned meaning, and Y represents an oxygen or sulphur atom. A purely thermal condensation cannot usually be successfully carried out with the acid amides, which, in turn, are produced, for example, by reduction of suitable nitro compounds, but it can rather in the case of the thioamides, which are obtained, for example, by treating the acid amides with phosphoric pentasulphide and do not require to be isolated prior to the subsequent condensation. Especially in the case of the acid amides it is useful to work in the presence of condensing agents, for example phosphoric pentachloride, phosphoroxychloride, phosgene or polyphosphoric acid. It is to be supposed that the ring closure involved goes partly through intermediate stages, like imide chlorides, amide chlorides, imidophosphates, amidophosphates or salt-like derivatives thereof, which can not generally be isolated. Condensation of the thioamides may be aided by the presence of mercury salts or by intermediate formation of (if desired activated) imido thio ethers. Heating and, if required, the use of an inert diluent are useful when working with phosphoroxychloride and phosphoric pentachloride, as also the addition of catalytic amounts of dimethylformamide or dimethylaniline.

Compounds in accordance with this invention can further be prepared by reacting primary amines of the formula:



(VIII),

wherein R_4 and R_5 have the above-mentioned meaning, or derivatives thereof, which are lower monoalkylated in the amino group, with reactive esters of alcohols having the formulae:



(IX),

wherein R, R_1, R_2, and R_3 have the meaning identified above, for instance with hydrohalic, carbonic, sulphonic, or *p*-toluene sulphonic acid esters, if desired under prior or simultaneous action by a basic catalyst or metallizing agent like sodium amide, lithium-amide, sodium hydride, butyl lithium, phenyl sodium, sodium ethylate or potassium-t-butylate. The primary amines of formula VIII are obtained by treating a reaction mixture containing nitrilium or imonium cations of formulae II with ammonia.

In so far as by one of these processes compounds are obtained, wherein one or several of the residues R_1, R_2 and R_3 denote hydrogen, substituents, R_1 and/or R_2 and/or R_3 other than hydrogen may subsequently be introduced by reaction of the primary or secondary amines with reactive esters of alcohols of the formula

$$R_1\text{—OH or } R_2\text{—OH or } R_3\text{—OH,}$$

respectively, using the same methods as described above.

The bases (I) obtained in the manner just described are in most cases crystallizable, otherwise they can be distilled under high vacuum without decomposition, and they form with inorganic and organic acids, e.g. hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, acetic, oxalic, tartaric and toluene-sulphonic acid, addition salts which are stable in water and in which form the products can likewise be used.

The 6-basic substituted morphanthridines and their acid-addition salts described above are new compounds which are used as active substances in medicines or as intermediates for the manufacture of such substances. In particular the products are of interest as neuroplegics, neuroleptics and analgesics. Some of them are suitable for the treatment of psychotic conditions. This utility is manifested pharmacologically by considerable depression of motility in mice, which may be accompanied by cataleptic action. The motility depressing action can be shown by measuring the locomotor activity in accordance with the method of Caviezel and Baillod [Pharm. Acta Helv. *33*, 469 (1958)]. In the following Table I, the locomotor activity obtained with some compounds of this invention, as well as their toxicity, are compared with the corresponding data of chloropromazine.

TABLE I

Active substance	Toxicity (mouse) LD 50 mg/kg p.o.	Locomotor activity (mouse) ED 50 mg/kg p.o.
Chloropromazine	135	3,5
6-(4-Methyl-1-piperazinyl)-morphanthridine	415	1,7
6-(4-Methyl-1-piperazinyl)-8-chloro-morphanthridine	180	0,18
3-Chloro-6-(4-methyl-1-piperazinyl)-morphanthridine	530	4,6

The compounds of this invention can be administered in the form of pharmaceutical preparations containing, besides the active substance, organic or inorganic solid or liquid carriers suitable for enteral or parenteral administration. The pharmaceutical preparations may be, for exmple, in the form of tablets, dragees, or solutions for injection in ampoule form, one dosage unit containing from 1 to 50 mg of active substance, depending on its nature, on the route of administration and on the physician's prescription, the effective daily dose amounting to from 10 to 500 mg of active substance.

EXAMPLE 1.

A mixture of 4.9 gm of 5,6-dihydro-6-oxo-morphanthridine, 37 ml of phosphoroxychloride and 1.5 ml of dimethylaniline is heated for three hours at reflux. The viscous oil, obtained by evaporation of the reaction mixture *in vacuo* at 60°C., is diluted with 20 ml of absolute dioxane and, after adding 30 ml of N-methylpiperazine, heated for 4 hours at reflux. The resulting clear solution is evaporated *in vacuo* at 60°C. to dryness. The residue is distributed between ether and ammonia water. The ethereal solution is separated, washed with water and then extracted with 1-n acetic acid. The acetic acid extract is mixed with ammonia water and then extracted with ether. The ethereal solution is washed with water, dried over sodium sulphate, filtered through alumina and evaporated. The residue is caused to crystallize from ether/petroleum ether, and recrystallized from acetone/petroleum ether. 6.0 gm (88% of the theory) of 6-(4-methyl-1-piperazinyl)-morphanthridine of melting point 138—138.5°C. are obtained.

The 5,6-dihydro-6-oxo-morphanthridine used as a starting material is usefully obtained in the following way:

30.2 gm of *o*-aminodiphenylmethane are dissolved in 65 ml of absolute toluene and, while stirring and at a temperature of between 0° and −10°C., 140 ml of 20% phosgene solution in toluene are added drop by drop. By bubbling phosgene slowly through it the milky mixture is heated within 30 minutes to reflux temperature, which is maintained during some 20 minutes. While stirring vigorously, dry nitrogen is passed into the boiling reaction mixture for 10 minutes. After evaporation of the solvent there are obtained by vacuum distillation 29.7 gm (86% of the theory of *o*-isocyanatodiphenylmethane of boiling point 169°C./12 mm Hg.

21.1 gm of aluminium chloride are heated in 110 ml of *o*-dichlorobenzene to 80°C. and, while stirring, a solution of 29.7 gm of *o*-isocyanatodiphenylmethane in 60 ml of *o*-dichlorobenzene is added drop by drop, whereupon the temperature of the mixture rises to 120°C. This temperature is maintained for one hour while stirring. After

cooling the reaction mixture is poured into 200 ml of 2-N hydrochloric acid, whereupon a brown precipitate is formed. After steam distillation the residue is isolated by filtration and crystallized from acetone/water. There are obtained 28.6 gm (97% of the theory) of 5,6-dihydro-6-oxo-morphanthridine of melting point 201—203°C.

EXAMPLE 2.

10 ml of N,N-dimethylaniline are poured over 33.5 gm of 5,6-dihydro-6-oxo-morphanthridine and, after adding 300 ml of phosphoroxychloride, heated for 4 hours under reflux. The reaction mixture is evaporated *in vacuo*. The residue is suspended in absolute xylol. The residue obtained by evaporating the suspension *in vacuo*, is taken up in ether and poured over ice/water. The ethereal phase is separated and washed 3 times with dilute hydrochloric acid, the hydrochloric washing water being rewashed with ether. The combined ether phases are successively washed with water, sodium bicarbonate solution, water and saturated sodium chloride solution, dried over sodium sulphate, treated with active charcoal, filtered through alumina and largely concentrated by evaporation. Upon adding petroleum ether there are obtained 30.2 gm (83% of the theory) of 6-chloromorphanthridine in the form of yellowish prisms of melting point 149—151°C.

7.5 gm of the 6-chloromorphanthridine thus obtained are heated in 100 ml of absolute xylol with 15 ml of N,N-dimethylaminoethylamine for 4 hours under reflux. The reaction mixture is mixed with water and concentrated soda lye. The aqueous phase is separated and washed with ether, and the ether used for washing is combined with the xylol phase. The organic phase is exhaustively extracted with dilute hydrochloric acid. The combined acid extracts are washed with ether, made alkaline with concentrated soda lye and then extracted with ether. The ethereal extract is washed with water and saturated sodium chloride solution, dried over sodium sulphate, treated with active charcoal and evaporated. The residue is taken up in petroleum ether. The solution is filtered through alumina and largely concentrated by evaporation. When the concentrated solution cools down white crystals are formed. There are obtained 7.2 gm of 6-(β-dimethylaminoethylamino)-morphanthridine of melting point 92—94°C.

EXAMPLE 3.

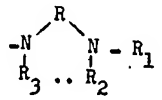
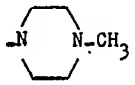
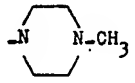
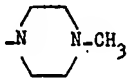
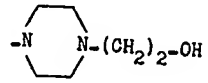
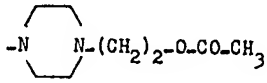
6.7 gm of *o*-[(4-methyl-1-piperazinyl)carboxamido]diphenylmethane are heated with 75 ml of phosphoroxychloride for 30 hours under reflux. The reaction mixture is evaporated *in vacuo* to dryness. While being cooled the residue is mixed with water and made alkaline with concentrated soda lye. The ethereal extract obtained by shaking twice with ether is washed twice with water and then exhaustively extracted with dilute hydrochloric acid. The combined hydrochloric extracts are washed with ether, made alkaline with concentrated soda lye and extracted twice with ether. The ethereal extract is washed with water and saturated sodium chloride solution, dried over sodium sulphate, filtered through alumina and evaporated. The residue is crystallized from petroleum ether. 3.0 gm of 6-(4-methyl-1-piperazinyl)-morphanthridine of melting point 138—138.5°C. are obtained. This product is identical to that of Example 1.

EXAMPLE 4.

16.6 gm of 2-amino-diphenylmethane-2¹-thiocarboxylic acid(4-methyl)piperazide are boiled under reflux with 17.0 gm of finely powdered mercuriacetate in 200 ml xylene during 24 hours. The reaction mixture is filtered and the filtrate is extracted with dilute acetic acid. The acid solution is treated with ammonia and extracted with ether. The ethereal solution is washed with water, dried over sodium sulphate, filtered through alumina and evaporated. The residue is crystallized from petroleum ether. 8.7 gm of 6-(4-methyl-1-piperazinyl)-morphanthridine of melting point 138—138.5°C. are obtained; the product is identical to that of Example 1.

In a like manner as in the Examples previously mentioned there are obtained from the corresponding starting materials the products listed in the following Table II. R, R_1, R_2, R_3, R_4, and R_5 have the same meaning as mentioned above. In the last column A means acetone, C chloroform, E ether, and P petroleum ether.

TABLE II

Ex.		R_4, R_5	Physical constants
5		8—Cl	m.p. of the base: 135—137 °C (from E/P)
6		3—Cl	m.p. of the base: 202—204 °C (from C/P)
7		2—Cl	m.p. of the base: 163—164.5 °C (from E/P)
8	—NH—$(CH_2)_3$—$N(CH_3)_2$	H	m.p. of the base: 110—111 °C (from E/P)
9		H	m.p. of the base: 143—145 °C (from A/P)
10		H	m.p. of the base: 105—107 °C (from A/P)
11	—$N(CH_3)$—$(CH_2)_3$—$N(CH_3)_2$	H	m.p. of the hydrochloride: 223—225 °C (from methanol/E) b.p. of the the base: 155—160°C/0,05 mm Hg.
12		H	b.p. of the base: 170—175 °C/0,07 mm Hg m.p. of the base: 110—111 °C (from A/E)
13	—NH—$(CH_2)_2$—NH_2	H	m.p. of the base: 122—125 °C (from acetic acid ester/E)

EXAMPLE 14.

Production of tablets

For the manufacture of tablets, the products of this invention can be mixed with lactose and granulated with water, 0.5% sodium alginate or 1% gelatine solution. The dried granulate is compressed into tablets in the presence of about 5% of talcum, 5% of corn starch and 0.1% of magnesium stearate. In this way, there are obtained, e.g. tablets of the following composition:

A)

6-(4-Methyl-1-piperazinyl)-8-chloromorphanthridine	10 mg
Lactose	80 mg
Corn starch	5 mg
Talcum	5 mg
Magnesium stearate	0.1 mg

These 100 mg tablets possess psycholeptic action. They are administered orally in a dosage of 3 to 6 tablets per day in the treatment of patients suffering from psychotic excitement.

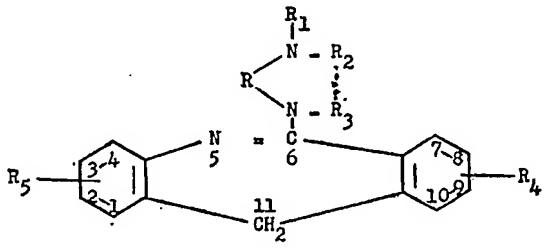
B)

6-(4-Methyl-1-piperazinyl)-morphanthridine	30 mg
Lactose	160 mg
Corn starch	10 mg
Talcum	10 mg
Magnesium stearate	0.2 mg

These 210 mg tablets possess psycholeptic action. They are administered orally in a dosage of 5 to 10 tablets per day in the treatment of conditions of psychotic excitement.

WHAT WE CLAIM IS:—

1. 6-basic substituted morphanthridines of the formula:



and physiologically acceptable acid addition salts thereof, in which R denotes a straight or branched chain alkylene group having not more than 5 carbon atoms, R_1 denotes a hydrogen atom or lower alkyl, lower hydroxyalkyl, acylated lower hydroxyalkyl or alkoxyalkyl group having not more than 5 carbon atoms, R_2 and R_3, which may be the same or different denote hydrogen, lower alkyl, or, when taken together, an ethylene group, and R_4 and R_5 which may be the same or different denote hydrogen or halogen.

2. Compounds as claimed in claim 1 in which the basic substituent in the 6-position is the 4-methyl-1-piperazinyl residue.

3. 6-(4-Methyl-1-piperazinyl)-morphanthridine.

4. 3-Chloro-6-(4-methyl-1-piperazinyl)morphanthridine.

5. 6-(4-methyl-1-piperazinyl)-8-chloro-morphanthridine.

6. Compounds as claimed in claim 1, other than those claimed in claims 3 to 5, the preparation of which is described in any of the Examples.

7. Pharmaceutical compositions containing one or more compounds as claimed in claim 1 in association with a pharmaceutically acceptable carrier.

8. Compositions as claimed in claim 7 in unit dosage form, for example as tablets, dragees or as injectable solutions in ampoule form, each dosage unit containing from 1 to 50 mg of active ingredient.

9. Compositions as claimed in claim 8 substantially as herein described with reference to Example 14.

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